

## Fatty Acid Metabolism I--11/4/02

### Study Questions:

1) Having fasted overnight, describe the major routes now operating in the body for catabolizing fuel compounds. Include the hormonal controls of these pathways.

The intent of this question is to get to the point where you have clearly exhausted your glycogen stores and are dependent on lipolysis to produce FAs (for  $\beta$ -oxidation) and glycerol (for gluconeogenesis) and on protein breakdown to produce alanine (that can be converted into pyruvate in the liver and used for gluconeogenesis). Let's ignore the nitrogen metabolism for now (the protein), because you will have that later in the course in more detail than I can provide here. Lipolysis is stimulated by a decrease in the insulin to glucagon ratio. Normally, it is about 0.5 in the fed state and about 0.15 after an overnight fast. A low insulin to glucagon ratio stimulates lipolysis. The glucagon acts at its receptor on the adipose cell to activate adenylate cyclase and hence cAMP-dependent protein kinase. cAMP-dependent protein kinase phosphorylates hormone sensitive lipase. The phosphorylated form of hormone sensitive lipase is active and it will hydrolyze the position 1 and 2 ester linkages that connect the fatty acids to the glycerol backbone of triacylglycerol. Monoacylglycerol lipase cleaves the last ester linkage to release another FA and free glycerol. Because adipose lacks glycerol 3-kinase, both the FA and the glycerol diffuse into the plasma. FAs are carried by serum albumin to muscle where they are used for energy production by  $\beta$ -oxidation and to the liver where they are used to generate ketone bodies for export to other tissues as a fuel source and for energy production by  $\beta$ -oxidation. The glycerol is transported to the liver where it is used for gluconeogenesis. A very small amount of both the glycerol and the FAs will be used by the liver to produce TGs to maintain a minimal amount of VLDL production as well.

2) List the four repeating steps of  $\beta$ -oxidation, in order, with the correct enzyme names and ATP yields (if any) for each step.

- a. Oxidation of a fatty acyl CoA by acyl CoA dehydrogenase to produce a *trans*  $\Delta^2$  fatty enoyl CoA. FAD is the electron acceptor in this reaction. This reaction yields 1.5 ATP.
- b. Hydration of the  $C_2=C_3$  double bond by enoyl CoA hydratase to produce L- $\Delta^3$ -hydroxyacyl CoA. Water is consumed in this reaction.
- c. Oxidation of the L- $\Delta^3$ -hydroxyacyl CoA by L-3-hydroxyacyl CoA dehydrogenase to produce a  $\Delta^3$ -ketoacyl CoA. NAD<sup>+</sup> is the electron acceptor in this reaction. This reaction yields 2.5 ATP.
- d. Thiolysis of the  $\Delta^3$ -ketoacyl CoA by  $\Delta^3$ -ketothiolase to produce acetyl CoA and a fatty acyl CoA that is two carbon atoms shorter than it began the cycle with. The S of the -SH group of CoA is the nucleophile in this reaction.

How many ATP do you produce when you completely oxidize one molecule of acetyl CoA?

10 ATP for just the acetyl CoA.

For one round of  $\Delta^2$ -oxidation, the yield is 14 ATP for a fully saturated fatty acid. You get one molecule of FADH<sub>2</sub> (1.5 ATP) and one molecule of NADH (2.5 ATP) and one molecule of acetyl CoA (10 ATP) for one round of  $\Delta^2$ -oxidation. Remember, in the TCA cycle, one molecule of acetyl CoA yields 3 NADH (7.5 ATP), 1 FADH<sub>2</sub> (1.5 ATP) and one GTP (the equivalent of 1 ATP).

**3) What two additional enzymes do you need to oxidize fatty acids with odd and even numbered carbon-carbon double bonds?**

An isomerase and a 2, 4-dienoyl reductase.

Which are used for each type of double bond? The isomerase deals with the odd numbered C=C double bonds. During  $\Delta^2$ -oxidation, odd numbered C=C double bonds will form a *cis*  $\Delta^3$  C=C double bond intermediate and the isomerase converts this to a *trans*  $\Delta^2$  C=C double bond that is a substrate for the enoyl CoA reductase. You

end up skipping the acyl CoA dehydrogenase step in this case and lose 1.5 ATP to deal with this type of double bond

You need both the 2, 4-dienoyl reductase and the isomerase to deal with even numbered C=C double bonds. With even numbered C=C double bonds you go through the acyl CoA dehydrogenase step but are left with a 2, 4-dienoyl intermediate that is not a substrate for the enoyl reductase. To deal with this, the C=C double bonds are reduced to yield a *trans* 3 C=C double bond intermediate and then the isomerase rearranges this to the *trans* 2 C=C conformation that is a substrate for the enoyl reductase. Because it consumes one molecule of NADPH to reduce the double bond and because it takes 2.5 ATP to build an NADPH molecule in the pentose phosphate shunt, this lowers the effective yield of ATP produced by  $\beta$ -oxidation of an even numbered C=C double bond by 2.5 ATP.

#### 4) Why is fat a good storage form of metabolic energy?

Fat is a good storage form of metabolic energy because on a per gram basis it is 6 times more efficient than storing metabolic energy as carbohydrate or protein. The reason for this is because fatty acids are more reduced than carbohydrate or protein and because fat is stored anhydrously as triacylglycerols (fat) in adipose tissue. Both carbohydrates and proteins are more oxidized than fatty acids and can therefore yield less ATP in the metabolic pathways (glycolysis and TCA cycle) per carbon atom. For example, on a dry weight basis alone, fat yields 9 kcal/gram (beta-oxidation and TCA cycle) whereas protein and carbs yield 4 kcal/gram. Now this difference is not 6-fold. The reason its 6-fold **as stored** is because carbohydrates and proteins are stored surrounded by water that takes up extra mass. Once you take this into consideration, you can store 6 times as many calories as fat per gram as you can as carbohydrates or proteins per gram.